ARIC Manuscript Proposal #2307

PC Reviewed: 2/11/14 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Socioeconomic status and incidence of subclinical myocardial damage

b. Abbreviated Title (Length 26 characters): **SES and Troponin**

2. Writing Group:
Writing group members:

Anna Fretz; Andrea L.C. Schneider; John (Bill) W. McEvoy; Ron C. Hoogeveen; Christie M. Ballantyne; Josef Coresh; Elizabeth Selvin; others Welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AF **[please confirm with your initials electronically or in writing]**

F**irst author**: **Anna Fretz**
Address: Welch Center for Prevention, Epidemiology, and Clinical Research
Johns Hopkins Bloomberg School of Public Health
2024 E. Monument St., Suite 2-600
Baltimore, MD 21287

Phone: 510-356-7113 Fax: 410-955-0476
E-mail: afretz1@jhu.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Elizabeth Selvin
Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E. Monument Street, Suite 2-600
Baltimore, MD 21287

Phone: 410-614-3752 Fax: 410-955-0476
E-mail: lselvin@jhsph.edu

3. Timeline: Data is currently available. Analysis is planned to start as soon as approval is obtained and will take between 3 and 6 months. Manuscript will be prepared during the 3 months following the completion of the analysis.

4. Rationale:

There is a well-established association between socioeconomic status (SES) and risk of cardiovascular disease (CVD) events (2,10,12,15,16,18,22). This relationship is not fully explained by health-related behaviors, lifestyle factors, or traditional CVD risk factors (10,12,15,18,22). There is also a growing literature on SES as a risk factor for subclinical measures of CVD, such as carotid intima-media thickness (4,9,14,23) and coronary artery calcification (17,20,26). However, the association between SES and these measures of atherosclerotic vascular disease are not consistent (4,9,14,17,20), suggesting that non-atherosclerotic mechanisms may also be an important contributor to CVD events.

Indeed, there is evidence that SES is independently associated with hypertension (10,11,12,28) and microvascular dysfunction (12,13), but only weakly or non-significantly associated with dyslipidemia (13,19). The existing literature on SES and CVD suggests that chronic stressors in daily life, indicative of low socioeconomic status, result in maladaptive physiologic coping mechanisms and elevated allostatic load, a heightened coping state of the body continually responding to stressors, causing stress-induced physiologic injury. These pathways damage the body through microvascular dysfunction and increased blood pressure as well as reduce the body's ability to return to homeostatis following an acute stressor, causing persistent allostatic elevation (11,25,27). In light of this literature, as well as the much stronger relationship between SES and CVD compared to SES and subclinical CVD, as measured by atherosclerotic markers IMT and CAC, the mechanism by which SES is associated with CVD may not be primarily atherosclerotic. This warrants the exploration of other potential mechanisms, such as myocardial injury, as measured by hs-cTnT, in the SES-CVD association.

New highly sensitive (pre-commercial) assays for cardiac troponin T (hs-cTnT) can detect cardiac troponin T at levels roughly ten times lower than the conventional assay (6) and indicate subclinical myocardial damage. Recent studies have demonstrated that very low levels of hs-cTnT are prevalent in a large portion of the general population and even these low, previously undetectable levels, are associated with significant cardiovascular risk (6,7,24). Interestingly, hs-cTnT is most predictive of incident HF and cardiovascular mortality and is less related to coronary heart disease. Indeed, hs-cTnT is strongly associated with microvascular risk factors (e.g. hypertension) and only weakly associated with traditional atherosclerotic risk factors (e.g. total and LDL-cholesterol). The current literature suggests that the association between hs-cTnT and cardiovascular outcomes may be more strongly mediated by other mechanism(s) distinct from atherosclerosis of the epicardial coronary vessels (5,6,7,24). The primary objective of the proposed study is to determine whether SES is associated with subclinical myocardial injury, as measured by hs-cTnT. As a secondary objective, we will also examine whether socioeconomic factors partially or wholly mediate the well-established higher levels of hs-cTnT among African Americans as compared to whites (6,29), This research may help

inform the underlying mechanism(s) by which socioeconomic status is associated with cardiovascular disease.

5. Main Hypothesis/Study Questions:

Aim 1. To evaluate the prospective association between baseline socioeconomic status, as measured by income, education, and lifetime occupation, and the incidence of subclinical myocardial damage during 6 years of follow-up (from visit 2 to visit 4). Our primary outcome will be the incidence of elevated hs-cTnT (>=14 ng/L) at visit 4 (among persons without elevated hs-cTnT at visit 2). We will also conduct analyses to examine associations with incident detectable hs-cTnT (>=5 ng/L) among persons without detectable levels at baseline (visit 2). These associations will be evaluated before and after adjustment for traditional cardiovascular risk factors.

> Hypothesis: Lower socioeconomic status will be prospectively associated with greater incidence of subclinical myocardial damage.

Aim 2. To evaluate whether socioeconomic status helps to explain the established racial differences in hs-cTnT. We will examine whether comprehensive adjustment for socioeconomics factors partially or fully explains the higher mean levels of hs-cTnT at baseline in blacks compared to whites and faster progression of subclinical myocardial damage during prospective follow-up.

> Hypothesis 2: Socioeconomic factors will partially explain the racial disparity in hs-cTnT, between African Americans and Whites.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design: Prospective analysis of SES measures and hs-cTnT measured at two time points, 6 years apart (ARIC visits 2 and 4). Visit 2 will serve as baseline for the present study. We will also examine the cross-sectional and prospective associations between race and hs-cTnT to evaluate whether adjustment for baseline SES factors explain the higher mean levels of hs-cTnT at baseline in blacks compared to whites and also the greater progression to elevated hs-cTnT in blacks compared to whites during the 6 years of follow-up in the ARIC Study.

Study Population (Inclusion/Exclusion Criteria):
All ARIC participants who attended visits 2 and 4 and who did not meet any of the following exclusion criteria:
-MI, angina, stroke, or revascularization before visit 2
-Missing hs-cTnT value at visits 2 or 4
-Missing education or income information at visit 1
-Missing lifetime occupation at visit 4 (will be used as a surrogate for lifetime occupation at visit 2)
-Identify as non-white race in Minnesota or Maryland
-Identify as non-black race in Mississippi

Exposure:
We will characterize socioeconomic status using three different variables: income (HOM62), education (HOM54) and occupation (SESA10A). Income is defined as: total combined family income for the past 12 months, with 9 possible responses represented by the categories below. Education is defined as: highest grade or year of school completed, with possible answers ranging from 0 to 23, as well as missing. Occupation is defined as: occupation for the longest time period, with 9 possible responses, representing the categories below. These three measures, income, education and occupation, are most commonly used, either alone or in combination, to measure socioeconomic status (22). Income, defined as total combined family income in the past 12 months, and education, defined as highest grade or year of school completed, are both collected at visit 1. Occupation, defined as occupation for the longest time period, was collected at visit 4, however given that it measures occupation over the life course, we think it is reasonable to use this variable as a proxy for visit 2 occupational status.

For the analysis, we will look at SES by each variable categorically as well as an SES z-score.

For looking at each SES variable, the SES variables will be categorized as follows:

Income will be divided into 9 categories: less than $5,000; $5,000-$7,999; $8,000-$11,999; $12,000-$15,999; $16,000-$24,999; $25,000-$34,999; $35,000-$49,999; over $50,000. The two lowest income categories (less than $5,000 and $5,000-$7,999 may be combined in the final analysis if numbers are too small. Moreover, in assessing race-specific strata, other income groups within the races may become too small, and in such a case we would combine categories of race-specific income groups to maintain adequate power, as suggested elsewhere (9). For those with missing income data, they will be categorized as “unknown income” and included in the analysis to maintain statistical power.

Education will be divided into 7 categories: no high school (less than 8 years), some high school (8-11 years), high school or GED (12 years), some vocational school, some college, college degree, graduate or professional school. For those with missing education

data, they will be categorized as "unknown" yet included in the analysis to maintain statistical power.

Occupation will be divided into 7 categories based on the 2000 US Census categorization: management and professional occupations (I); sales and office occupations (II); service occupations (III); farming, fishing and forestry occupations (IV); construction, extraction and maintenance occupations (V); production, transportation and material moving occupations (VI). For those with missing occupation data, they will be categorized as "unknown" (VII) yet included in the analysis to maintain statistical power.

In a sensitivity analysis, we will also look at each SES variable modeled as a z-score, in order to compare magnitudes of association across the different variables.

Outcome:

Cardiac troponin T was measured using a highly-sensitive novel (pre-commercial) assay, Elecsys Troponin T (Roche Diagnostics, Indianapolis, Indiana). For the purposes of these analyses, we will define 5.0 ng/L as the lower limit of detection (3,8) although we will conduct sensitivity analyses using the lowest level of measurability (3.0 ng/L). The assay demonstrated between-assay coefficients of 2.6% for control materials with mean cTnT concentration of 2378 ng/L and 6.9% for control materials with mean cTnT concentration of 29 ng/L. Laboratory reliability was 0.99 in participants with HF and 0.94 in participants without HF (1); reliability coefficient was assessed to be r=0.98 with a coefficient of variation of 15% after excluding outliers of greater than SD from the mean (24). Serum samples were drawn at visit 2 and plasma samples were drawn at visit 4. These samples were stored at -80° until time of assay, which was 2011 for visit 4 plasma samples and 2013 for visit 2 serum samples. Literature demonstrates high correlation between visit 2 serum and visit 4 plasma (21).

Covariates:

Age (years, continuous), sex (male/female), race/field center (Maryland whites; Minnesota whites, North Carolina whites; North Carolina blacks; Mississippi blacks), body mass index (continuous), diabetes (yes/no), total cholesterol (continuous), HDL cholesterol (continuous), systolic and diastolic blood pressure (continuous), blood pressure medication use (yes/no), smoking (current/former/never), alcohol consumption (current/former/never), physical activity (categorical, visit 1), LV hypertrophy (yes/no), IMT (continuous). All measured at baseline visit 2, unless otherwise noted.

Statistical Analysis:

For the primary analysis, we will consider hs-cTnT in a binary fashion. The primary outcome will be incident elevated hs-cTnT (>=14ng/L) at visit 4 from non-elevated hs-cTnT (<14ng/L) at visit 2. We will also look at the prospective association of 6-year change in hs-cTnT, with change defined as incident detectable cardiac troponin T

(>=5ng/L) at visit 4 from non-detectable (<5ng/L) at visit 2. For these binary outcomes we will use Poisson regression to generate adjusted risk ratios.

We will perform three statistical models:

- Model 1: adjust for demographic factors (age, gender, race/field center [only if not a modifier], other SES variables not used as exposure)
- Model 2: Model 1 + additional cardiovascular risk factors (total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, blood pressure medication use, diabetes, CRP, eGFR)
- Model 3: Model 2 + behavioral factors (physical activity, alcohol consumption, smoking, BMI)

Since race may be the most important modifier in the relationship between SES and hs-cTnT, we will do an analysis to determine its influence by running a statistical model looking at the relationship between race and hs-cTnT with and without the three SES variables and quantify the magnitude of changes in the regression coefficient for race.

Sensitivity Analyses:
We will perform four sensitivity analyses:

1) Sensitivity analysis modeling hs-cTnT continuously, imputing hs-cTnT levels that are undetectable as 1.5ng/L, half of the lower limit of blank detection of the Roche assay. Moreover, we will also use a lower limit of detection of 3ng/L, as hs-cTnT levels between 3-5ng/L can incur important risk information.
2) Sensitivity analysis for the prospective association imputing hs-cTnT values at visit 4 for those who died between visit 2 and visit 4 (and thus do not have hs-cTnT measurements at visit 4) as events in the Poisson analyses with assigned values of 60.0ng/L in the continuous analyses, since elevated hs-cTnT has been shown to be associated with all-cause mortality (6,24).
3) Sensitivity analysis using the most recent occupation variable from visit 1, OCCUPN01, instead of lifetime occupation from visit 4, SES10A, and see if the regression coefficient for occupation changes.
4) Sensitivity analysis modeling SES variables as Z-scores and potentially combining them to form a global Z-score if associations are similar and pooling is reasonable.
5. Sensitivity analysis using data only from North Carolina to assess race-field center aliasing.

Potential effect modifiers:
We will test for interaction by age, race, and sex. A stratified analysis will be performed if statistically significant effect modification for any of the mediators is observed.

Limitations:

We are limited by the two measurements of hs-cTnT at visit 2 and then visit 4, which are two years apart, as a means of characterizing the progression of subclinical myocardial injury. As well, with socioeconomic status as a highly complex exposure, perhaps the ideal measure would be to combine various factors (e.g., income, educational attainment, father's educational attainment, mother's educational attainment, and lifetime occupation) into a type of SES score, however there is widespread use of SES measured as income, education and occupation separately in the literature and for a basic analysis of SES with baseline (visit 2) hs-cTnT and prospective change in hs-cTnT, we feel that our measurement of SES is appropriate. There also may be considerable effect of geography on race, considering African Americans are only sampled from two sites (~90% from Mississippi and remaining 10% from North Carolina), however we will perform a sensitivity analysis using data from only the one site with both African Americans and Whites, North Carolina, to elucidate race-field center aliasing. Using the lower limit of detection with reliability as 5.0 ng/L, a considerable portion of the participants will have undetectable hs-cTnT levels and we are thus required to impute them as half of the lower limit of detection for the sensitivity analysis, however this imputation is imperfect. Also, the imputation of hs-cTnT levels for those who died between visit 2 and visit 4 for the sensitivity analysis, is not ideal. Lastly, because this is an observational study only, we cannot rule out the potential of confounding.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?
____ Yes _X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

9. **The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

_X_ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MS #1563: Novel highly sensitive cardiac Troponin-T (hs-cTnT) assay, mortality, and major adverse cardiovascular events in the ARIC Study (Saunders)

MS #2025: Obesity and Subclinical Myocardial Injury: The Atherosclerosis Risk in Communities (ARIC) Study (Ndumele)

MS #2269: Risk factors for Progression of Subclinical Myocardial Injury: Six-year change in highly-sensitive troponin T in a community-based population study (McEvoy)

MS #1759: Associations of traditional cardiovascular risk factors and high-sensitivity cardiac troponin T (Rubin)

MS #1757: The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD (Nambi)

MS #1734: Biomarker, anthropometric parameters associated with highly sensitive cardiac troponin T (Nambi)

MS #2002: Association of High-Sensitivity Cardiac Troponin T (hs-cTnT) with Cognitive Function: the Atherosclerosis Risk in Communities Study (Schnieder)

MS #1811: Association of high sensitive Troponin T (hs-cTnT),N- Terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause- specific mortality: ARIC study (Oluleye)

MS #1808: The utility high sensitivity cardiac troponin t in the prediction of heart failure risk (Nambi)

MS #926: Individual and Area-Level Lifecourse Socioeconomic Status and Subclinical Atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study (Carson)

MS #472: The role of major cardiovascular risk factors in the relationship of SES with atherosclerosis (Greiser)

MS #385: Socioeconomic Status and Incident Coronary Heart Disease (Massing)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X_ Yes ____ No

ARIC Ancillary Study #2008.10: Measurement of NT-pro-BNP and troponin T at visit 4 for the full ARIC cohort (Ballantyne)

ARIC Ancillary Study #2009.16: Short-term Markers of Glycemia and Long-term Outcomes (Selvin)

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* #2008.10, #2009.16)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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